REMARKS / ARGUMENTS

The Claims

Applicants have cancelled Claims 23-40 and substituted new Claims 41-58. The new claims are fully supported by the specification and do not raise issues of new matter or new considerations requiring further consideration and/or search. New claims have been introduced to place them in better condition for allowance or appeal. Accordingly, Applicant respectfully request entry of the claims.

Claim 40 is objected to as being an improper multiple dependent claim. Introduction of new claims render this object moot.

Rejections under 35 U.S.C. 112

Claims 23-40 are rejected under 35 U.S.C. 112, second paragraph, as it is maintained that the term "lytic bone disease" is alleged to be unclear. Introduction of the new claims renders this rejection moot.

Claims 23-30 and 35-40 are rejected under 35 U.S.C. 112, first paragraph as the specification is alleged to lack enablement for the claimed subject matter. In spite of the numerous examples pointed out by Applicant of the use of unfused OPG to prevent or treat bone loss, the Examiner alleges that the claims are overly broad by encompassing any OPG and any truncated polypeptides of OPG. The Examiner also argues that Claim 30 encompasses OPG fused to any polypeptide, which is alleged to be not enabled by the specification. The Examiner argues that the specification allegedly does not enable prevention of bone loss or abnormal bone formation.

Applicant submit that the rejection is moot in view of the new claims. However, Applicant points out that the rejection of the claims as overly broad by encompassing any OPG or any truncated OPG polypeptide is a new grounds for rejection which was not necessitated by amendment nor based on information submitted in an information disclosure statement. The Examiner previously argued in the Office Action dated March 14, 2001 that the specification was not enabling and did not provide working examples for unfused OPG. Applicant pointed out in the response dated September 14, 2001 that unfused OPG polypeptides may be used in the prevention and treatment of bone loss as evidenced by the data shown in Table 1 of PCT publication no. WO97/23614. Now, the Examiner has decided that the examples of unfused OPG polypeptides do not enable any OPG polypeptide or truncated OPG polypeptide. This ground for rejection was not set forth in any previous Office Action and therefore should either be withdrawn or submitted as part of a non-final Office Action. However, even if the Examiner should maintain the rejection as final, Applicant submits that the examples of unfused OPG polypeptides enable the full scope of the claims and the Examiner has not provided any evidence to the contrary.

The Examiner maintains that the claims are not enabled for prevention of bone loss as the specification provides no guidance as to when OPG would be administered in order to prevent a lytic bone disease.

The Examiner has argued that " ... a patient would ordinarily have no idea that he has lytic bone disease, until after-the-fact." Moreover, the Examiner argues that the Lodish reference (cited as Reference V on PTO-892) states that " ... tumors are significantly progressed before they become discernible." However, the Lodish reference and the Conte reference cited below in the rejection under 35 U.S.C. 103(a) both strongly suggest the opposite conclusion. On p. 43 of the Conte reference, it is stated that " ... up to 70% of patients with advanced breast cancer develop lytic bone metastases". In addition, the Lodish reference (p. 1055, right hand column), states that "[s]ome malignant tumors remain localized and encapsulated, at least for some time ... ". Taken together, the references make it clear that malignant (or metatstatic) tumors can be detected before they have metastasized and that there was a high probability of metastasis to bone. Therefore, one skilled in the art would readily conclude that patients can be diagnosed as being susceptible to lytic bone disease and would be candidates for treatment with OPG.

As indicated in the specification at p. 2, lines 2-9, formation of abnormal bone is accompanied by an increase in osteoclast bone destruction during bone metastases. The specification is enabling for prevention of abnormal bone formation for the same reasons as set forth in the previous paragraph.

The Examiner also argues that the art is unpredictable. Sternson (cited as Reference X on form PTO-892) is alleged to teach that significant obstacles to delivery of unmodified proteins for therapeutic needs. This argument is moot in view of the evidence previously cited that administration of unfused OPG polypeptides show prevention and treatment of bone loss. Even assuming for the sake of argument that the art is unpredictable, Applicant has overcome this by working examples of unfused OPG polypeptides.

It is also argued that the specification allegedly does not enable the subject matter of Claim 30 relating to OPG fusion polypeptides. It is believed that this rejection is moot in view of the new claims.

Applicant maintains that the claimed subject matter is enabled by the specification and the rejection should be withdrawn.

Rejection under 35 U.S.C. 103

Claims 23-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boyle et al. (WO97/23614) in view of Conte et al. (Annals of Oncology 5:S41-S44 (1994) or Simonet et al. (Cell 89, 309-319 (1997)). The Examiner alleges that the feature of "treating bone loss due to cancer" is not recited in Claim 23 and therefore cannot be relied upon to argue nonobviousness. The Examiner also argues that the combined references would have motivated one to combine OPG with a chemotherapeutic agent to treat bone loss.

It is believed that the new claims render the rejection moot. Moreover, Applicant reiterates his previous argument that there is no motivation to combine the references in order to arrive at the claimed invention. Conte et al. report the results of a clinical trial involving patients with lytic bone metastases receiving a combination of pamidronate and chemotherapy. Pamidronate (sold under the brand name Areida®) is a member of a class of compounds called bisphosphonates which are distinct from OPG polypeptides and appear to affect bone

metabolism by a different mechanism than OPG. There was no suggestion that one could or should use a completely different anti-resorptive bone agent in combination with a cancer therapy agent for lytic bone disease in view of the results obtained with the bisphosponate, pamidronate. Indeed, Conte states on p. S44 that "[f]uture research will focus on comparative trials with other bisphosphonates ... ", indicating that, at best, the results in Conte suggest trying other compounds in the same class. Applicant respectfully requests that the rejection be withdrawn.

CONCLUSION

Claims 41-58 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Plasmids encoding OPG[1-194]-Fc, OPG[1-201]-Fc, OPG[1-194]-FcΔC, OPG[1-201]-FcΔC, OPG[1-194]-FcG_{10}, and metFcΔC-OPG[22-194] for use in producing the corresponding OPG fusion polypeptides are constructed generally as described in WO97/23614 and in copending U.S. Serial No. 09/389,545, filed September 3, 1999, both of which are incorporated by reference. The polypeptide sequences are shown in Figures 3-8, respectively.